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PLoS GENETICS

Novel Loci for Adiponectin Levels and Their Influence on Type 2 Diabetes and Metabolic Traits: A Multi-Ethnic Meta-Analysis of 45,891 Individuals

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Abstract

Circulating levels of adiponectin, a hormone produced predominantly by adipocytes, are highly heritable and are inversely associated with type 2 diabetes mellitus (T2D) and other metabolic traits. We conducted a meta-analysis of genome-wide association studies in 39,883 individuals of European ancestry to identify genes associated with metabolic disease. We identified 8 novel loci associated with adiponectin levels and confirmed 2 previously reported loci ($P = 4.5\times10^{-8}$–1.2×10^{-43}). Using a novel method to combine data across ethnicities (N = 4,232 African Americans, N = 1,776 Asians, and N = 29,347 Europeans), we identified two additional novel loci. Expression analyses of 436 human adipocyte samples revealed that mRNA levels of 18 genes at candidate regions were associated with adiponectin concentrations after accounting for multiple testing ($p<3\times10^{-4}$). We next developed a multi-SNP genotypic risk score to test the association of adiponectin decreasing risk alleles on metabolic traits and diseases using consortia-level meta-analytic data. This risk score was associated with increased risk of T2D ($p = 4.3\times10^{-3}$, n = 22,044), increased triglycerides ($p = 2.6\times10^{-14}$, n = 93,440), increased waist-to-hip ratio ($p = 1.8\times10^{-5}$, n = 77,167), increased glucose two hours post oral glucose tolerance testing ($p = 4.4\times10^{-3}$, n = 15,234), increased fasting insulin ($p = 0.015$, n = 48,238), but with lower in HDL-cholesterol concentrations ($p = 4.5\times10^{-13}$, n = 96,748) and decreased BMI ($p = 1.4\times10^{-4}$, n = 121,335). These findings identify novel genetic determinants of adiponectin levels, which, taken together, influence risk of T2D and markers of insulin resistance.

Citation: Dastani Z, Hivert M-F, Timpson N, Perry JRB, Yuan X, et al. (2012) Novel Loci for Adiponectin Levels and Their Influence on Type 2 Diabetes and Metabolic Traits: A Multi-Ethnic Meta-Analysis of 45,891 Individuals. PLoS Genet 8(3): e1002607. doi:10.1371/journal.pgen.1002607

Editor: Peter M. Visscher, The University of Queensland, Australia

Received September 30, 2011; **Accepted** February 3, 2012; **Published** March 29, 2012

Funding: Baltimore Longitudinal Study of Aging (BLSA): The BLSA was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. A portion of that support was through an R&D contract with MedStar Research Institute. Erasmus Rucphen Family (ERF). The ERF study was supported by grants from The Netherlands Organisation for Scientific Research, Erasmus MC and the Centre for Medical Systems Biology (CMSB), and the European Network for Genetic and Genomic Epidemiology (ENGAGE) consortium. Invecchaire in Chianti (InCHIANTI). JRB Perry is a Sir Henry Wellcome Postdoctoral Research Fellow (092447/Z/10/Z). Framingham Heart Study (FHS): This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. The Collaborative Health Research in the Region of Augsburg (KORA F3): This study was partially funded by the ''Tiroler Wissenschaftsfonds'' (Project UNI-0407/29) and by the ''Genomics of Lipid-associated Disorders – GOLD'' of the ''Austrian Genome Research Programme GEN-AU'' to F Kronenberg. The MONICA/KORA Augsburg cohort study was financed by the Helmholtz Zentrum München. It was further funded by the NIH subcontract from the Children's Hospital, Boston, US, (H-E Wichmann and IM Heid, prime grant 1 R01 DK075787-01A1 to JN Hirschhorn) and the German National Genome Research Net NGFN2 and NGFNplus (H-E Wichmann 01GS0823). TwinsUK: Study was funded by the Wellcome Trust, European Commission Framework (FP7/2007–2013), ENGAGE project HEALTH-F4-2007-201413, and the FP5 GenomEUtwin Project (QLG2-CT-2002-01254). It also receives support from the Arthritis Research Campaign, Chronic Disease Research Foundation, the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London, and a Biotechnology and Biological Sciences Research Council project grant (G20234). Cardiovascular Health Study (CHS): The CHS research reported in this article was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, grant numbers U01 HL080295 and R01 HL087652, HL105756, and HL094555 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. DNA handling and genotyping was supported in part by National Center for Research Resources grant M01-RR00425 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center, NHLBI R01-HL085251. Helsinki Birth Cohort Study (HBCS): HBCS has been supported by grants from Academy of Finland (project numbers 114382, 126775, 127437, 129255, 129306, 130326, 209072, 210595, 213225, 216374), Finnish Diabetes Research Society, Finnish Foundation for Pediatric Research, Samfundet Folkhälsan, Juho Vainio Foundation, Novo Nordisk Foundation, Finska Läkaresällskapet, Päivikki and Sakari Sohlberg Foundation, Signe and Ane Gyllenberg Foundation, and Yrjö Jahnsson Foundation. DILGOM survey was funded by the Finnish Academy, grant number 118065. Cardiovascular Risk in Young Finns (YFS): The Young Finns Study has been financially supported by the Academy of Finland: grants 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi), the Social Insurance Institution of Finland, Kuopio, Tampere and Turku University Hospital Medical Funds, Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research (T.L., OT.R), Tampere Tuberculosis Foundation (Te.Le., Mik, Kä), the Emil Aaltonen Foundation (T.L.) and Finnish Cultural Foundation. The expert technical assistance in the statistical analyses by Irina Lisinen and Ville Aalto are gratefully acknowledged. Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM): K Kristiansson was supported by the Orion-Farmos Research Foundation and the Academy of Finland (grant no. 125973). M Perola and V Salomaa were supported by the Finnish Foundation for Cardiovascular Research, the Sigrid Jusélius Foundation, and the Academy of Finland (grants 129322, 129494 and 139635). JG Eriksson was supported by the Academy of Finland (grants 126775, 129255, 129907, and 135072). Fenland study: The Fenland Study is funded by the Wellcome Trust and the Medical Research Council, as well as by the Support for Science Funding programme and CamStrad. We are grateful to all the volunteers for their time and help, and to the General Practitioners and practice staff for help with recruitment. We thank the Fenland Study co-ordination team and the Field Epidemiology team of the MRC Epidemiology Unit for recruitment and clinical testing. Multiethnic Study of Atherosclerosis (MESA): The MESA project is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support is provided by grants and contracts N01 HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, and RR-024156. Funding for CARe genotyping was provided by NHLBI Contract N01-HC-65226. Jackson Heart Study (JHS): The Jackson Heart Study is supported by the National Heart, Lung, and Blood Institute, through contracts with Jackson State University (N01-HC-95170), the University of Mississippi Medical Center (N01-HC-95171), and Tougaloo College (N01-HC-95172). Adiponectin measurements used in the current study were funded by PHS Award UL1 RR025008 from the Clinical and Translational Science Award program, National Institutes of Health, National Center for Research Resources (NCRR). Health ABC: This research was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106. The genome-wide association study was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. Genetics, Arthrosis , and Progression) study (GARP): This study was supported the Leiden University Medical Centre and the Dutch Arthritis Association. Pfizer, Groton, CT, USA supported the inclusion of the GARP study. The genotypic work was supported by the Netherlands Organization of Scientific Research (MW 904-61-095, 911-03-016, 917 66344 and 911-03-012), Leiden University Medical Centre and the Centre of Medical System Biology and Netherlands Consortium for Healthy Aging both in the framework of the Netherlands Genomics Initiative (NGI). The adiponectin measurements were supported by TI-Pharma. Atherosclerosis Risk in Communities (ARIC): The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, R01HL087641, R01HL59367, R01HL086694, and RC2 HL102419; National Human Genome Research Institute contract U01HG004402; National Institutes of Health contract HHSN268200625226C; and National Institute of Diabetes and Digestive and Kidney Diseases R01DK056918. Infrastructure was partly supported by Grant Number UL1RR025005,a component of the National Institutes of Health and NIH Roadmap for Medical Research. Salzburg Atherosclerosis Prevention Program in subjects at High Individual Risk (SHAPIR): Part of this work was funded by the ''Genomics of Lipid-associated Disorders'' (GOLD) of the ''Austrian Genome Research Programme'' (GEN-AU) to Florian Kronenberg, and grants from the ''Medizinische Forschungsgesellschaft Salzburg'' and the ''Kamillo Eisner Stiftung'' (Switzerland) to Bernhard Paulweber. THISEAS: The genotyping of the THISEAS study was funded by the Wellcome Trust. The recruitment was partially supported by the General Secretary of Research and Technology (PENED 03<EPSILON><DELTA>474). We are grateful to all the volunteers for their time and help, the medical staff of the hospitals and the field investigators, Eirini Theodoraki, Maria Dimitriou and Kathy Stirrups for her assistance in the genotyping. Cebu Longitudinal Health and Nutrition Survey (CLHNS): We thank the Office of Population Studies Foundation research and data collection teams and the study participants who generously provided their time for this study. This work was supported by National Institutes of Health grants DK078150, TW05596, HL085144, RR20649, ES10126, and DK56350. Coordinating Centre: McGill University. This work was supported by grants from the Canadian Foundation for Innovation, the Canadian Institutes of Health Research (CIHR), Fonds de la recherche en santé du Québec, the Lady Davis Institute, the Ministère du Développement économique, de l'Innovation et de l'Exportation du Québec and the Jewish General Hospital. JB Richards and Z Dastani are supported by the CIHR. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: DM Waterworth, X Yuan, and VE Mooser are full-time employees of GlaxoSmithKline. P Vollenweider received grant money from GlaxoSmithKline to fund the CoLaus study. The other authors declare no competing financial interests.

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‡ Memberships of these consortia are provided in the Acknowledgments.

Introduction

Adiponectin is a highly abundant adipocyte-derived plasma protein whose levels correlate inversely with a range of important clinical parameters including blood glucose, indices of insulin resistance, proatherogenic dyslipidemia, and risk of type 2 diabetes (T2D), stroke and coronary artery disease [1,2,3,4]. Collectively these conditions account for most of the burgeoning pandemic of

Author Summary

Serum adiponectin levels are highly heritable and are inversely correlated with the risk of type 2 diabetes (T2D), coronary artery disease, stroke, and several metabolic traits. To identify common genetic variants associated with adiponectin levels and risk of T2D and metabolic traits, we conducted a meta-analysis of genome-wide association studies of 45,891 multi-ethnic individuals. In addition to confirming that variants at the *ADIPOQ* and *CDH13* loci influence adiponectin levels, our analyses revealed that 10 new loci also affecting circulating adiponectin levels. We demonstrated that expression levels of several genes in these candidate regions are associated with serum adiponectin levels. Using a powerful novel method to assess the contribution of the identified variants with other traits using summary-level results from large-scale GWAS consortia, we provide evidence that the risk alleles for adiponectin are associated with deleterious changes in T2D risk and metabolic syndrome traits (triglycerides, HDL, post-prandial glucose, insulin, and waist-to-hip ratio), demonstrating that the identified loci, taken together, impact upon metabolic disease.

obesity-related morbidity and mortality that poses a severe and global healthcare challenge [5]. Murine studies suggest that adiponectin plays a mediating role in at least some of these obesity-related complications, and although less clearly established in humans, this suggests that understanding the pathophysiology of adiponectin may uncover novel therapeutic targets in major, highly prevalent human disease.[6,7].

Twins and family studies have revealed moderate to high estimates of heritability (30–70%) for plasma adiponectin levels [8,9,10,11]. However, until recently, few genes associated with adiponectin levels have been identified. Candidate and genome-wide association studies (GWAS) have shown pronounced associations between common polymorphisms in the adiponectin gene (*ADIPOQ*) and adiponectin levels [12,13,14,15]. A recent meta-analysis of three GWAS for adiponectin levels identified variants in a novel candidate gene, *ARL15*, that were associated with adiponectin levels, coronary heart disease (CHD), T2D and other metabolic traits [16]. Furthermore, *CDH13* and *KNG1* genes were found to be associated with adiponectin levels in two studies involving East Asian populations [17,18]. Although part of the variance explained by the *ADIPOQ* locus, most of the heritability of adiponectin levels remains unaccounted for. Therefore, we sought to identify novel common variants influencing adiponectin levels and test their association with risk of T2D and related metabolic traits within the framework of a large multi-ethnic consortium of GWAS.

We combined genome-wide association results of 35,355 individuals from three different ethnicities (white Europeans (n = 29,347), African American s(n = 4,232) and East Asians (n = 1,776)), applying a novel meta-analytic method to allow for heterogeneity in allelic effects between populations of different ethnic backgrounds. We next examined whether identified genome-wide significant single nucleotide polymorphisms (SNPs) also associated with expression of their nearest gene in human adipocytes, the main source of adiponectin. Since adiponectin has been associated with T2D, insulin resistance and metabolic traits we next investigated whether a multi-SNP genotypic risk, comprising genome-wide significant SNPs for adiponectin levels, also influenced risk of T2D and related traits measured in the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM+) [19], Meta-Analysis of Glucose and Insulin Related Traits Consortium (MAGIC) [20], Genetic Investigation of ANthropometric measures Traits (GIANT) [21] , Global Lipids Genetic Consortium (GLGC) [22], and Body Fat GWAS consortia [23].

Results

Results of Meta-Analysis of GWAS

The meta-analysis was divided into four phases 1) Discovery phase, which involved cohorts providing GWAS results, 2) In-silico replication phase which included additional GWAS cohorts joining our meta-analysis after the completion of the discovery phase, 3) De-novo genotyping in cohorts without GWAS genotyping and 4) Multi-Ethnic meta-analysis applying a novel method for complex trait mapping using different ethnicities.

Discovery phase in individuals of white European origin. The meta-analysis of sex-combined data from 16 GWAS (n = 29,347) of individuals of white European descent identified ten loci associated with adiponectin levels at $p \leq 5.0 \times 10^{-8}$ (Table 1 and Figure 1A and Figure S1, Table S2). These results include the previously described associations with adiponectin at *ADIPOQ* (rs6810075[T]; ß = 0.06, *p*-value = 3.60×10^{-41}), *KNG1* (rs2062632[T]; ß = 0.05, *p*-value = 2.52×10^{-19}) on 3q27.3, and *CDH13* (rs12922394[T; ß = −0.1, $p = 3.16 \times 10^{-18}$) on 16q23.3 (Table 1). Furthermore, we identified variants that showed genome-wide significant association in eight novel independent loci including rs9853056 (within the *STAB1 gene*, rs4282054 (within the *NT5DC2 gene*), rs13083798 (within the *PBRM1* gene), rs1108842 (within the *GNL3* gene), rs11235 (within the *NEK4* gene), rs2710323 (within the *ITIH1* gene), rs3617 (within the *ITIH3* gene), and rs2535627 (within 200 Kb of *ITIH4* gene) at 3p21.1; rs1597466 (within 1 Mb of *TSC22D2* gene) at 3q25.1; rs2980879 (within 1 Mb of *TRIB1* gene) at 8q24.13; rs7955516 (within 1.3 Mb *PDE3A* gene) at 12p12.2; rs601339 (within the *GPR109A* gene) at 12q24.31; rs6488898 (within the *ATP6V0A2* gene), rs7133378 (within *the DNAH10* gene), rs7305864 (within the *CCDC92* gene), and rs7978610 (within *the ZNF664* gene at 12q24.31, which is 1.3 Mb away from *GPR109A*); rs2925979 (within the *CMIP* at 16q23.2 gene); and rs731839 (within *the PEPD* gene) at 19q13.11. (Figure 2A–2E, Table 1).

In our analysis a common variant (rs601339, MAF = 0.18, allele G) downstream of the GPR109A gene (the putative niacin receptor) was associated with adiponectin (ß = 0.04, $p = 7.94 \times 10^{-10}$) and HDL-C (ß = 0.03, $p = 5.59 \times 10^{-7}$) in the global lipid analysis. In a coincident candidate gene analysis 11 SNPs were typed in GPR109A/B in CoLaus and LOLIPOP cohorts, containing individuals of European descent. A single nominally significant coding SNP R311C (rs7314976, MAF = 0.14) within the GPR109A gene was taken forward for replication and found to be consistently associated with adiponectin in the three cohorts (CoLaus, Fenland and MRC Ely study, n = 8285, $p = 4.6 \times 10^{-8}$) and HDL-cholesterol (HDL-C) in four cohorts (CoLaus, Fenland, Ely study and Lolipop, n = 18425, $p = 2.9 \times 10^{-8}$) (Figure S2A, S2B). However R311C and rs601339 were not in linkage disequilibirium with each other (r2 = 0.04). Therefore the two variants represent two independent signals from the same locus but with similar effects on HDL-cholesterol and adiponectin.

In silico follow-up phase. In the *in-silico* follow-up phase 468 SNPs demonstrating genome-wide significant ($p < 5 \times 10^{-8}$) or suggestive ($p < 5 \times 10^{-6}$) association with adiponectin in the discovery phase were tested for association in additional European cohorts. (Table S3). These SNPs were tested in seven additional GWAS datasets (n = 6,623 from NHS, HPFS, HABC, ERF2, LLS, GARP and ARIC studies) and the combined meta-

Table 1. Lead SNP per Locus for Genome-Wide Significant SNPs Arising from the Sex-Combined Meta-Analysis in European Populations.

Nearest** Gene	Lead SNP‡	Region	Chr/position†	EA/NEA¶	EAF¶¶	Beta§	SE	P	I2	n	Beta§	SE	P	I2	n
						Discovery Phase Results					Joint Analysis Phase*				
LYPLAL1	*rs3001032*	*1q41*	*1/217794402*	*T/C*	*0.7*	*−0.02*	*0.005*	*1.98E-06*	*0*	*29,321*	*−0.02*	*0.004*	*3.60E-08*	*0*	*35,930*
GNL3	*rs1108842*	*3p21.1*	*3/52695120*	*C/A*	*0.50*	*0.03*	*0.004*	*3.66E-11*	*0.33*	*29,338*	*0.03*	*0.004*	*1.39E-13*	*0.2*	*35,962*
TSC22D2	rs1597466	3q25.1	3/151538251	T/G	0.1	−0.04	0.008	1.88E-08	0	29,319	−0.03	0.007	1.62E-06	0.1	35,794
ADIPOQ	*rs6810075*	*3q27.3*	*3/188031259*	*T/C*	*0.6*	*0.06*	*0.005*	*3.60E-41*	*0*	*29,140*	*0.06*	*0.004*	*1.19E-43*	*0*	*35,749*
VEGFA	*rs998584*	*6q21.1*	*6/43865874*	*C/A*	*0.5*	*0.03*	*0.005*	*5.84E-08*	*0.3*	*28,167*	*0.03*	*0.005*	*3.25E-08*	*0.2*	*34,108*
TRIB1	*rs2980879*	*8q24.13*	*8/126550657*	*T/A*	*0.7*	*0.03*	*0.005*	*1.08E-08*	*0*	*24,084*	*0.03*	*0.005*	*7.13E-09*	*0*	*30,708*
PDE3A	*rs7955516*	*12q12.2*	*12/20389303*	*C/A*	*0.4*	*0.03*	*0.005*	*2.43E-08*	*0.1*	*29,178*	*0.02*	*0.004*	*4.45E-08*	*0*	*38,276*
GPR109A	*rs601339*	*12q24.31*	*12/121740696*	*G/A*	*0.2*	*0.04*	*0.006*	*3.87E-11*	*0*	*29,325*	*0.03*	*0.005*	*7.81E-10*	*0.3*	*35,947*
DNAH10	rs7133378	12q24.31	12/122975455	G/A	0.7	−0.03	0.005	1.29E-09	0	29,223	−0.02	0.004	6.21E-07	0.5	35,697
CMIP	*rs2925979*	*16q23.2*	*16/80092291*	*T/C*	*0.3*	*−0.04*	*0.005*	*1.87E-18*	*0*	*29,347*	*−0.04*	*0.005*	*1.21E-20*	*0*	*35,970*
CDH13	*rs12922394*	*16q23.3*	*16/81229828*	*T/C*	*0.1*	*−0.10*	*0.011*	*3.16E-18*	*0.3*	*24,466*	*−0.08*	*0.010*	*1.99E-15*	*0.4*	*31,089*
PEPD	*rs731839*	*19q13.11*	*19/38590905*	*G/A*	*0.35*	*−0.04*	*0.005*	*2.20E-13*	*0.03*	*29,166*	*−0.03*	*0.004*	*7.97E-12*	*0.4*	*35,771*

All SNPs achieving genome-wide significance in the joint analysis phase are marked in italics.
*Joint analysis indicates results from the meta-analysis of discovery and follow-up *in-silico* and *de-novo* phases.
**When possible, plausible biological candidate genes have been listed; otherwise, the closest gene is designated.
‡Lead SNP is the SNP with the lowest *p*-value for each locus.
§Betas are estimated from models using the natural log transformed adiponectin.
¶EA: Effect allele, NEA: Non-effect allele.
¶¶EAF: Effect allele frequency.
doi:10.1371/journal.pgen.1002607.t001

analysis of the discovery and follow-up *in-silico* GWAS datasets detected additional loci on chromosomes 1q41 near the *LYPLAL1* gene (rs3001032, $p = 3.6\times10^{-8}$) and chromosome 6p21.1 near the *VEGFA* gene (rs998584, $p = 5.8\times10^{-12}$) that reached genome-wide significance. While we confirmed seven loci that had reached genome-wide significance at the discovery stage (Table 1, Figure 2F and 2G, Table S2), two identified loci (3q25.1 and 12q24.31) did not remain genome-wide significant in the joint analysis of discovery and follow-up results.

De novo follow-up phase. Next, in the *de-novo* genotyping follow-up phase, we genotyped 10 SNPs with suggestive evidence of association ($5\times10^{-8}<p<5\times10^{-6}$) from the meta-analysis of the discovery and *in-silico* follow-up phases in an additional 3,913 individuals. Meta-analyzing the discovery and 2 follow-up stages identified a SNP in *ARL15* (rs6450176 [G]; ß = 0.026, $p = 5.8\times10^{-8}$), which was initially described in a previous GWAS for adiponectin levels (Table S3) [16].

Multi-ethnic meta-analysis. To identify loci influencing adiponectin levels in non-European individuals we performed an additional analysis in 4,232 individuals from an African American population and 1,776 individuals from an East Asian population. In the African American populations, only associations at the *ADIPOQ* locus reached genome-wide significance, while in the East Asian population there was evidence of association at the *ADIPOQ* and *CDH13* loci (Table S4). Subsequently, we performed a meta-analysis that combined all available GWAS including those of white European origin, African American and East Asian ancestry using novel method MANTRA [24]. This analysis identified two additional loci in or near *IRS1 gene* on 2q36.3 and at 6q24.1 within a gene desert. (Table 2, Figure 1B).

Secondary GWAS analyses. We next performed meta-analysis of the GWAS data in women (n = 16,685) and men (n = 12,662) separately (Figure S2A, S2B, Tables S5 and S6). Although no novel loci reached genome-wide significance in women or men separately, three loci (chromosome 3p, 8 and 12) associated with adiponectin levels in the sex-combined analysis showed evidence of association (p value$<5\times10-8$) in women (Figure S3). Since different assays were used to measure adiponectin levels, we next tested whether stratification by assay rendered similar results and found the results were highly concordant with the combined analysis. GWAS for high molecular weight adiponectin in the CHS study (n = 2,718) identified 2 SNPs in *ADIPOQ* (rs17300539, $p = 3.0\times10^{-16}$) and *CMIP* (rs2927307, $p = 2.7\times10^{-8}$). These two genes are located within the loci identified in our discovery meta-analysis of adiponectin levels.

Gene Expression Studies

Through gene expression studies we sought to address two questions: First, are any of the SNPs that were genome-wide significant for adiponectin levels associated with expression of their nearest transcripts (*cis*-eQTLs) and second, whether mRNA levels of loci identified through the GWAS for adiponectin levels are associated with circulating adiponectin levels. To address the first question, we examined whether SNPs within 1 Mb of the SNPs achieving genome-wide significance in the discovery stage were associated with the expression levels of nearby genes in human adipocytes from 776 participants of the MuTHER Consortium [25]. We identified 74 SNPs in three eQTLs to be associated with the expression of five genes in adipocytes, using an array-wide level of statistical significance for eQTLs ($P<5.1\times10^{-5}$. See Materials and Methods for details). These genes included: *NT5DC2* on chromosome 3; *CCDC92*, *GPR109A*, and *ZNF664* on chromosome12; and *PEPD* on chromosome 19 (Table 3). The *cis*-eQTL

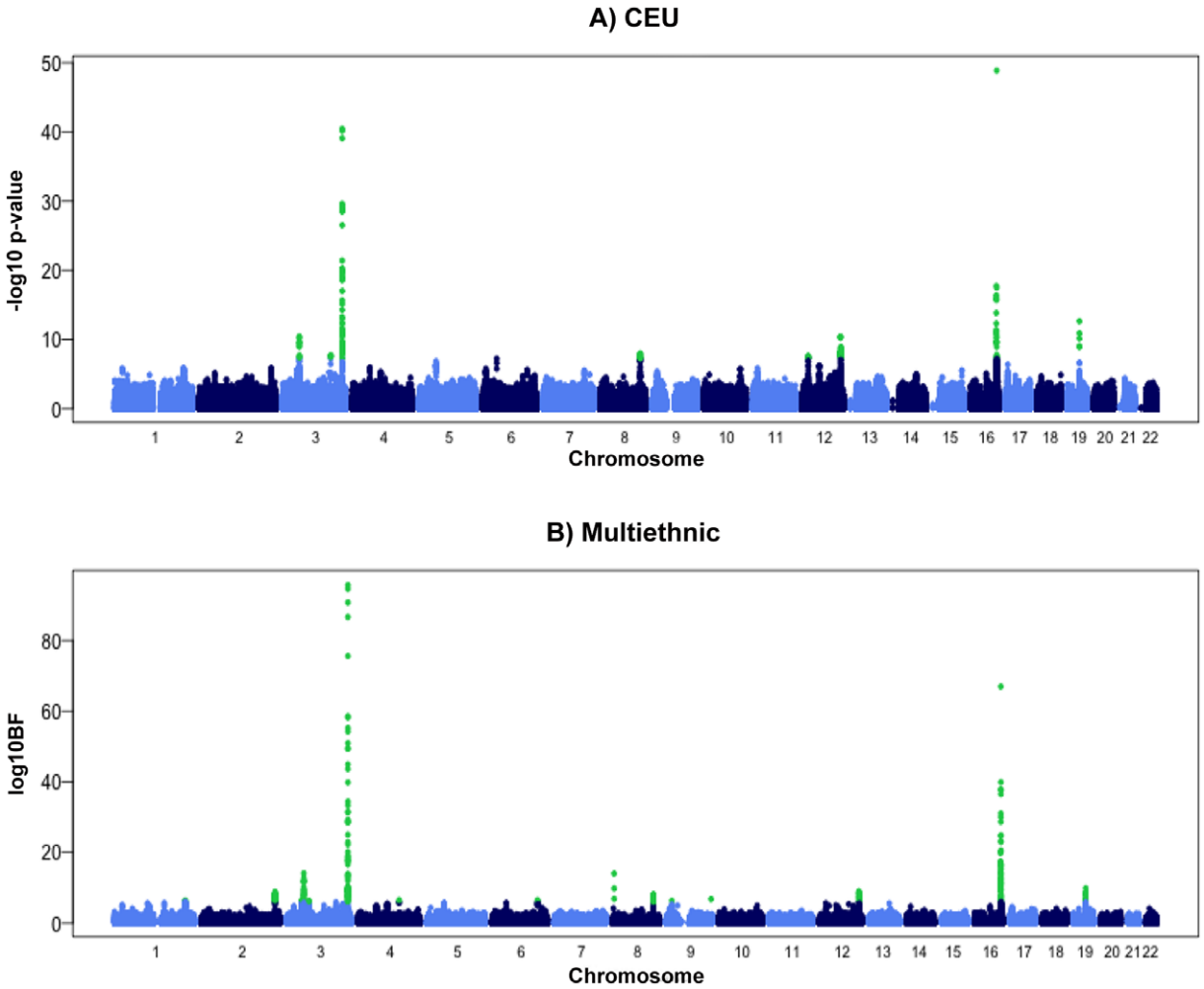

Figure 1. Manhattan plots for meta-analyses in the discovery phase. A) Combined sex analysis in European populations, B) Meta-Analysis of Multiple Ethnicities. The Manhattan plots show $-\text{Log}_{10}$ (*p*-value) measures for association between single nucleotide polymorphisms (SNPs) and chromosomal position. The SNPs that achieved genome-wide significance are highlighted in green.
doi:10.1371/journal.pgen.1002607.g001

SNPs often are proxies for the lead SNPs from the GWAS, however, this relationship may also be influenced through mechanisms that are independent from gene expression, such as gene function.

We next identified that mRNA levels of 18 genes arising from six candidate loci were correlated with circulating adiponectin levels (Table 4). Since circulating adiponectin levels may be associated with a surplus of adipocyte transcripts we next tested for enrichment of signal from the candidate loci. There were 133 transcripts in the identified candidate regions, of which 8.2% (11/133) were associated with adiponectin levels at an array-wide level of significance ($p<2\times10^{-6}$), while 7.5% of the 24k probes on the entire array exceeded the same p-value threshold, indicating there was therefore no additional enrichment of signal at these candidate loci.

T2D and Metabolic Traits

Using data from several large-scale GWAS consortia, some of the significantly associated variants identified here demonstrated associations with T2D and its related traits (Table S7A, S7B, S7C, and S7D). Several individual SNPs showed evidence for association with T2D and various metabolic traits after accounting for the number of statistically independent SNPs (p-value threshold of 5×10^{-4}) among the SNPs that were genome-wide significant for adiponectin. These include associations with HDL-C (n = 104 SNPs), triglycerides (TG) (n = 65 SNPs), total cholesterol (TC, n = 12 SNPs), LDL-cholesterol (LDL–C, n = 11 SNPs), and waist-hip ratio (WHR) (n = 65 SNPs) [26]. (However, we note that since sample sizes are different across different consortia power to identify associations is not consistent.) Among these, coding and intronic variants in *STAB1* and *NT5DC2* genes were associated with WHR and HDL-C, while the variants 1 Mb near *TRIB1* were associated with all lipid traits. The coding and intronic variants ariants in the locus on chromosome 12 harboring *ZNF664*, *CCDC92*, and *DNAH10* showed evidence of association with WHR, HDL-C, and TG. Finally, variants in the *PEPD* gene were associated with TG.

We next calculated a multi-SNP genotypic risk score based genome-wide significant SNPs from the discovery phase. This multi-SNP genotypic risk score explained 5% of the variance of natural log-transformed adiponectin levels. We then tested the association of this risk score with risk of T2D and metabolic related traits. The multi-SNP genotypic risk score was associated with increased risk for T2D ($\beta = 0.3$, $p = 4.3\times10^{-3}$), where ß is the average additive effect of adiponectin-decreasing risk alleles on the

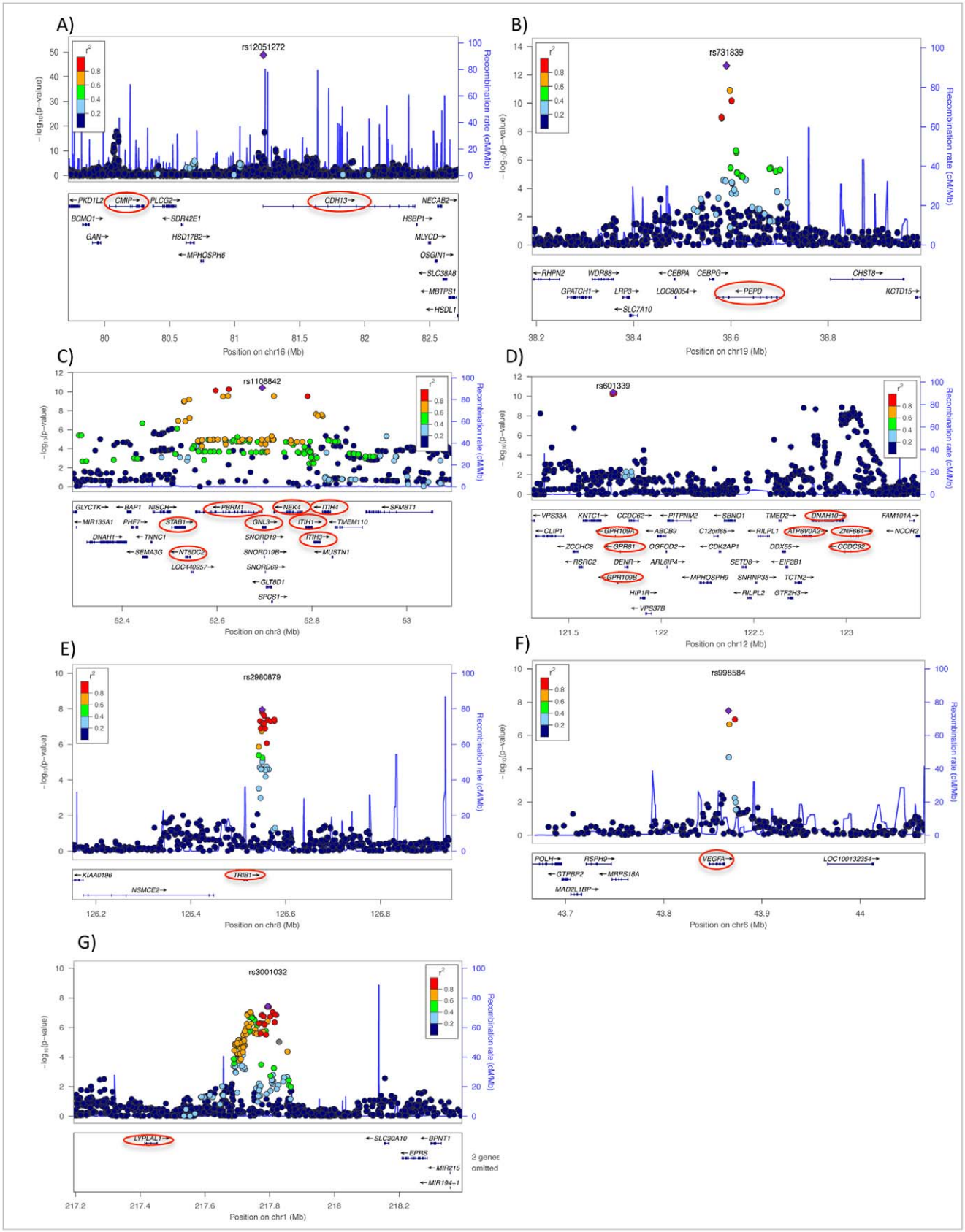

Figure 2. Regional plots of eight newly discovered genome-wide significant chromosomal regions associated with adiponectin concentrations in European populations. A) chromosome 16q23.2, B) chromosome 19 q13.11 C) Chromosome 3p21.1, D) two loci on chromosome 12q24.31, E) chromosome 8q24.13, F) chromosome 6p21.1, and G) chromosome 1q41. In each panel, purple diamonds indicate the top

SNPs, which have the strongest evidence of association. Each circle shows a SNP with a color scale relating the r^2 value for that SNP and the top SNP from HapMap CEU. Blue lines indicate estimated recombination rates from HapMap. The bottom panels illustrate the relative position of genes near each locus. Candidate genes are indicated by red ovals.
doi:10.1371/journal.pgen.1002607.g002

log odds ratio of T2D), increased TG (ß = 0.25, $p = 2.6\times10^{-14}$), increased WHR adjusted for BMI (ß = 0.18, $p = 1.8\times10^{-5}$), increased post-prandial glucose (ß = 0.25, $p = 0.01$), increased fasting insulin (ß = 0.05, $p = 0.01$), homeostatic model assessment-insulin resistance (HOMA-IR) (ß = 0.04, $p = 0.047$), and with lower HDL-C concentrations (ß = −0.24, $p = 4.5\times10^{-13}$) and decreased BMI (ß = −0.16, $p = 1.4\times10^{-4}$). (Table 5).

Discussion

In this comprehensive multi-ethnic analysis of the genetic influences on adiponectin levels and their impact on metabolic traits and T2D, we have identified 10 novel loci and confirmed the associations of variants in the *ADIPOQ* and *CDH13* loci with adiponectin levels. The adiponectin risk alleles were associated with T2D and related metabolic traits such as BMI, WHR, TG, HDL-C, 2-hour glucose, HOMA-IR and fasting insulin. These findings demonstrate that adiponectin, T2D and metabolic syndrome have a shared allelic architecture.

Biological Relevance of the GWAS Loci

In the first step toward understanding the biological relevance of the identified regions, we examined the genes harbored by the associated loci using human disease and animal databases. Although some of the genes in these loci do not have a known function, several signify diverse biological functions.

On chromosome 1, the lead SNP was located 300 kb from the *LYPLAL1*, a protein that regulates phospholipids on cellular membranes. Independent efforts have also identified this locus in other metabolic/obesity related traits GWAS: first with WHR (rs2605100; $r^2 = 0.49$ [21] and rs4846567; $r^2 = 0.55$ [27] respectively with the lead adiponectin SNP, rs3001032), and more recently with fasting insulin by a joint meta-analysis including the interaction between SNP and BMI (MF Hivert for the MAGIC investigators, personal communication). In the same report by MAGIC, variants near *IRS1* (insulin receptor substrate 1) and *PEPD* (a protein that hydrolyzes dipeptides and tripeptides) have also been associated with fasting insulin at genome wide significant levels, demonstrating a close link between adiponectin regulation and insulin resistance pathways. Moreover, both *IRS1* and *PEPD* have been associated with T2D (*IRS1* in DIAGRAM [28] and *PEPD* in a Japanese population [29]; $p = 9.3\times10^{-12}$ and $p = 1.4\times10^{-5}$, respectively).

The lead SNP at 3p21.1 falls within *GNL3* that is located in a genomic region containing many genes which could have potential functions in metabolism. Our data provide evidence that adiponectin levels were correlated with human adipocyte mRNA levels of many genes in this region (*GLYCTK*, *SEMA3G*, *STAB1*, *PBRM1*, *SFMBT1*; see Table 4). However, this association does not imply a direct influence of these genes on adiponectin level. Among those genes, *STAB1* encodes for stabilin 1, described as an endocytic receptor for advanced glycation end products and may have a function in angiogenesis, lymphocyte homing, cell adhesion, or receptor scavenging for acetylated low-density lipoprotein [30].

Interestingly, several of the genes near lead genome-wide significant SNPs have been implicated in angiogenesis, which might be important for adipose tissue expansion, highlighting the recurring theme of "adipose tissue expandability" in the genetic origins of obesity-related complications [31]. For example, *VEGFA* is the vascular endothelial growth factor A gene, a known gene in a variety of vascular endothelial cell functions, such as angiogenesis and maintenance of the glomerular endothelium in nephrons [32]. Variants in this gene are also associated with diabetic retinopathy and WHR [27,33]. Moreover, the product of *VEGFA* interacts with resveratrol, which has been shown to have a beneficial influence in some metabolic traits, including diabetes [34]. Rodent studies show that resveratrol decreases blood glucose, blood insulin, and glycated hemoglobin, as well as increases insulin sensitivity in animals with hyperglycemia (reviewed in [35]). Resveratrol also inhibits TNF-α-induced reductions in adiponectin levels in 3T3-L1 adipocytes [36]. Furthermore, it has been shown that resveratrol modulates adiponectin expression and improves insulin sensitivity, likely through the inhibition of inflammatory-like response in adipocytes [37]. At this locus, *VEGFA* mRNA levels in adipocytes were the strongest association with adiponectin levels (Table 4). Also likely involved in vascular biology, *TRIB1* encodes a G protein-coupled receptor-induced protein interacting with MAP kinases that regulates proliferation and chemotaxis of vascular smooth muscle cells [38]. *TRIB1* expression was shown to be elevated in human atherosclerotic arteries [39]. Several variants (rs2954029, rs2954021, rs17321515; all in moderate LD with our lead SNP) in the *TRIB1* gene have been associated with HDL-C, LDL-C and CHD risk in European and Asian populations [22,40,41,42,43]. These two loci (*TRIB1* and *VEGFA*) argue for the importance of vascular biology in adiponectin regulation as underlined previously by findings of adiponectin levels associated with variants near *CDH13* (a receptor for adiponectin expressed by endothelial smooth muscle) [44].

All three homologous genes *GPR109A/B/81* located on chromosome 12 are predominantly expressed in adipocytes and mediate antilipolytic effects [45]. Our eQTL results (Table 3) and the correlation between mRNA and adiponectin levels (Table 4) argue strongly for a role of *GPR109A* at this locus. *GPR109A* (also known as *NIACR1*) is a receptor with a high-affinity, concentration-dependent response to nicotinic acid (niacin) [45]. Treatment by niacin increases serum adiponectin levels by up to 94% in obese men with metabolic syndrome in a time- and dose-dependent manner [46]. Functional studies in *GPR109A* receptor knockout mice demonstrate that niacin increases serum total and HMW adiponectin concentrations and decreases lipolysis following *GPR109A* receptor activation [47]. Moreover, a recent meta-analysis on cohorts containing extremes of HDL-C provided evidence suggestive of association in *GPR109A/B/81* [48].

Finally, variants in *ZNF664* have been associated with CHD, HDL-C and TG levels in a large meta-analysis of over 100,000 individuals of European ancestry [22]. The sex heterogeneity observed in this study is comparable to our finding that the more loci associated with adiponectin at genome wide significance level have been shown in female stratified analysis.

Taken together, the loci identified in this large-scale GWAS for adiponectin levels highlight many genes with demonstrated relationships with metabolic disease.

Shared Allelic Architecture of Adiponectin Levels and Metabolic Traits

Using a multi-SNP genotypic risk score we attempted to understand if the allelic architecture of adiponectin levels was shared with T2D and metabolic traits. This risk score was

Table 2. Genome-Wide Significant SNPs from the Sex-Combined Multi-Ethnic Meta-Analysis.

Nearby* Gene	Lead SNP‡	Gene region	chr/position†	EA/NEA¶	EAF¶¶ (CEU/EA/AA)	Multi-Ethnic Fixed Effects Meta-analysis				Multi-Ethnic Random Effects Meta-analysis		MANTRA		N
						Beta (SE)	pvalue	Q-Value	I2	Beta (SE)	pvalue	BF§	phet††	
LYPLAL1	rs2791553	1q41	1/217742665	G/A	0.6/0.46/0.54	−0.02(0.004)	4.91E-07	25.18	0	−0.02(0.004)	4.91E-07	6.3	0.06	37,665
IRS1	**rs925735**	**2q36.3**	**2/226887874**	**G/C**	**0.64/0.89/0.74**	**−0.02(0.004)**	**1.88E-08**	**22.15**	**0.01**	**−0.02(0.004)**	**2.12E-08**	**8.1**	**0.06**	**37,638**
GNL3	rs2590838	3p21.1	3/52597126	G/A	0.5 1/0.34/0.54	−0.03(0.004)	4.08E-15	28.85	0.06	−0.03(0.004)	1.88E-13	14.1	0.05	37,680
ADIPOQ	rs6810075	3q27.3	3/188031259	T/C	0.93/1/0.86	0.06(0.004)	1.10E-43	27.44	0.02	0.06(0.004)	2.41E-42	43.6	0.16	31,533
-	**rs592423**	**6q24.1**	**6/139882386**	**C/A**	**0.54/0.36/0.41**	**0.02(0.004)**	**3.59E-07**	**15.46**	**0**	**0.02(0.004)**	**3.59E-07**	**6.5**	**0.03**	**37,430**
TRIB1	rs2980879	8q24.13	8/126550657	T/A	0.69/0.77/0.67	0.03(0.004)	9.91E-10	21.08	0	0.03(0.004)	9.91E-10	8.2	0.04	32,426
GPR109A	rs601339	12q24.31	12/121740696	G/A	0.19/0.39/0.31	0.03(0.005)	3.77E-09	36.11	0.25	0.03(0.006)	4.31E-06	8.3	0.09	37666
CMIP	rs2925979	16q23.2	16/80092291	T/C	0.3 0/0.43/0.31	−0.04(0.004)	3.12E-21	23.12	0	−0.04(0.004)	3.12E-21	19.8	0.31	37,687
CDH13	rs12051272	16q23.3	16/81220789	T/G	0.03/0.33/0.03	−0.26(0.017)	4.74E-51	39.17	0.62	−0.26(0.032)	1.10E-14	66.0	1.00	24,216
PEPD	rs4805885	19q13.11	19/38597963	T/C	0.39/0.64/0.41	−0.03(0.004)	1.65E-11	34.94	0.23	−0.03(0.005)	2.05E-08	9.9	0.05	37,479

The novel loci identified using Multi-Ethnic Meta-analysis (that were not identified in the European only analysis) are listed in **bold**.
*When possible, plausible biological candidate genes have been listed; otherwise, the closest gene is designated.
‡Lead SNP is the SNP with the lowest *p*-value for each locus.
†Positions are relative to Human Genome NCBI Build 36.
§$\log_{10}$ Bayes factor (BF) from the MANTRA analysis. A $\log_{10}$ BF of 6 and higher was considered as a conservative threshold for genome-wide significance.
††The posterior probability of heterogeneity between studies.
¶EA: effect allele, NEA: non-effect allele.
¶¶EAF: Frequency of effect allele in CEU, East Asian, and AA, populations respectively.
doi:10.1371/journal.pgen.1002607.t002

Table 3. The Association of Lead Genome-Wide Significant SNPs for Adiponectin with mRNA Levels of Their Nearest Gene.

Gene	Lead SNP-Cis-eQTL‡	Chr	Transcript Start Site	Transcript End Site	EA¶	EAF¶¶	Beta (SE)§	P-Exp*	P-GWAS**	lead SNP-GWAS‡‡	$r^2$$
NT5DC2	rs13081028	3	52533424	52544133	G	0.444	0.14(0.02)	1.32E-19	1.05E-09	rs1108842	0.84
GPR109A	rs2454722*	12	121778105	121781082	G	0.166	−0.15(0.03)	1.71E-09	3.87E-11	rs601339	1
CCDC92	rs10773049	12	122986907	123023116	T	0.611	0.15(0.02)	8.09E-22	2.67E-08	rs7133378	0.02
ZNF664	rs825453	12	123074711	123065922	T	0.615	−0.04(0.01)	4.51E-05	4.03E-08	rs7978610	0.03
PEPD	rs8182584	19	38569694	38704639	T	0.364	−0.13(0.02)	9.96E-10	6.64E-11	rs731839	1

‡Lead SNP is the SNP with the lowest *p*-value for each gene in gene expression data.
‡‡Lead SNP is the SNP with the lowest *p*-value for each locus in meta-analysis from discovery phase.
¶EA: Effect allele.
¶¶EAF: Frequency of effect allele.
§Betas are estimated expression levels of the genes.
*P value for lead SNP is the SNP in gene expression data.
**P value for lead SNP in meta-analysis from discovery phase.
$$r^2$ LD between lead SNP from expression and lead SNP from meta-analysis.
doi:10.1371/journal.pgen.1002607.t003

associated with increased risk of T2D and traits associated with insulin resistance and the metabolic syndrome. However, unexpectedly, adiponectin decreasing alleles were associated with a decrease in BMI. In our adiponectin GWAS, BMI was included as a covariate in order to avoid direct identification of obesity SNPs since BMI is strongly related to adiponectin levels [49,50]. Furthermore, this unexpected direction of effect was entirely explained by SNPs at the *ZNF664* and *PEPD* loci; when these loci were removed from the analysis, the association of the genotypic risk score with BMI disappeared (results not shown). Therefore, adiponectin risk alleles at *ZNF664* and *PEPD* are of considerable interest since they impart deleterious changes on aspects of the metabolic syndrome (increased TC, TG, LDL-C and WHR and decreased HDL-C), but also act to decrease BMI and percent fat.

Table 4. The Association of mRNA Levels from Genes in Candidate Loci in Human Adipocytes with Circulating Adiponectin Levels.

Gene	*Gene region*	GeneStart	GeneEnd	Beta§	Pvalue
GLYCTK	3p21.1	52296875	52304311	0.060	1.77E-20
SEMA3G	3p21.1	52442307	52454083	−0.018	9.28E-06
STAB1	3p21.1	52504395	52533551	−0.039	2.26E-14
PBRM1	3p21.1	52554407	52688779	0.007	2.49E-04
SFMBT1	3p21.1	52913666	53055110	0.010	2.53E-08
DNAJB11	3q27.3	187771160	187786283	−0.014	3.31E-07
EIF4A2	3q27.3	187984054	187990379	0.021	1.53E-08
ADIPOQ	3q27.3	188043156	188058944	0.054	1.03E-13
MAD2L1BP	6q21.1	43711554	43716666	0.009	4.09E-04
VEGFA	6q21.1	43845923	43862199	0.012	2.15E-09
ZCCHC8	12q24.31*	121523387	121551471	0.011	2.60E-04
GPR109B	12q24.31	121765255	121767392	0.010	3.74E-06
GPR109A	12q24.31	121778105	121781082	0.026	1.80E-11
PITPNM2	12q24.31*	122033979	122160928	−0.010	5.09E-06
U1SNRNPBP	12q24.31	122508604	122516894	0.011	1.72E-04
ATP6V0A2	12q24.31	122762817	122812252	−0.008	2.86E-04
ZNF664	12q24.31	123023622	123065922	0.010	8.28E-06
SLC7A10	19q13.11	38391409	38408596	0.072	1.66E-14

§Betas are estimated from log transformed and quantile-quantile normalized values.
*These two loci are independent loci.
doi:10.1371/journal.pgen.1002607.t004

Our data do not provide direct evidence as to whether the genetic determinants of adiponectin levels influence these traits through adiponectin itself, or through pleiotropic pathways and therefore do not constitute a Mendelian randomization study. These findings provide a note of caution for Mendelian randomization studies, which may be prone to erroneous conclusions if pleiotropic effects of tested variants are not considered. Nonetheless, in aggregate, these results provide strong evidence that the genetic determinants of adiponectin levels are shared with metabolic disease, and in particular, traits related to insulin resistance.

We note that there are several strengths and limitations of this study. Our main findings, identifying genetic determinants of adiponectin levels, are based on the largest meta-analysis to date and include results from three ethnicities. The availability of expression data from human adipose tissue permitted the association of identified SNPs with mRNA levels at candidate genes and, in turn, correlation of these mRNA levels with circulating adiponectin itself. While access to the data from large consortia permitted assessment of the relevance of the identified SNPs to T2D and components of the metabolic syndrome, we note that a subset of the cohorts included in our GWAS were also included in these external consortia. However, we note that even if we assume that all ADIPOGen study participants were included in the external consortia, for cohorts participating in both studies, that the majority of data in these external consortia still arises from study participants not present in ADIPOGen (minimum percent of non-overlapping subects: 86.8%, 85.5%, 86.4% and 82.5% for MAGIC, GLGC, GIANT, and DIAGRAM+ consortia, respectively). Therefore, since a substantial majority of participants are independent between ADIPOGen and these consortia, it is unlikely that our findings demonstrating a shared allelic architecture between adiponectin levels and these traits are spurious.

Further, we suggest that locus, 6q24.1, identified only through multi-ethnic meta-analysis using MANTRA and not confirmed through fixed and random effects meta-analysis, be replicated for confirmation of this finding.

In conclusion, the data presented in this study provide strong evidence of association for 10 novel loci for adiponectin levels.

Table 5. Results of Association of Multi-SNP Genotypic Risk Score with Diabetes and Related Traits.

Trait	N	Effect§ (95% CI)	P	Consortium
T2D**	**22,044**	**0.301 (0.09, 0.51)**	**4.3E-03**	**DIAGRAM+**
BMI (SD units)	**121,335**	**−0.162 (−0.25, −0.08)**	**1.4E-04**	**GIANT**
WHR*	**77,167**	**0.177 (0.1, 0.26)**	**1.8E-05**	**GIANT**
Percent Fat	34,853	−0.052 (−0.15, 0.05)	0.31	Body Fat Percent
Fasting Glucose (mmol/L)	46,186	0.011 (−0.03, 0.05)	0.58	MAGIC
Fasting Insulin(pmol/L)**	**38,238**	**0.05 (0.01, 0.09)**	**1.5E-02**	**MAGIC**
HomaB	36,466	0.033 (0, 0.07)	5.1E-02	MAGIC
Homa IR	**37,037**	**0.042 (0, 0.08)**	**4.7E-02**	**MAGIC**
2hr Glucose(mmol/L)**	**15,234**	**0.245 (0.06, 0.44)**	**1.1E-02**	**MAGIC**
HbA1C (%)	35,908	−0.002 (−0.04, 0.03)	0.91	MAGIC
TG(SD units)**	**93,440**	**0.248 (0.18, 0.31)**	**2.6E-14**	**GLGC**
HDL-C (SD units)**	**96,748**	**−0.243 (−0.31, −0.18)**	**4.5E-13**	**GLGC**
LDL-C (SD units)	92,348	0.023 (−0.05, 0.09)	0.52	GLGC
TC (SD units)	97,021	0.0003 (−0.07, 0.07)	0.99	GLGC

T2D: Type 2 diabetes, BMI: Body mass Index, WHR: Waist to hip ratio, HbA1C: hemoglobin A1C, TG: Triglyceride, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, TC: Total Cholesterol.
§Effect is mean change in trait or disease per adiponectin-decreasing allele.
*Waist to hip ratio adjusted for BMI.
**Significantly associated trait is coded in bold.
doi:10.1371/journal.pgen.1002607.t005

Further analyses confirmed that the level of expression of some of these candidate genes in human adipocytes correlated directly with adiponectin levels. A multi-SNP genotypic risk score, and several of the identified variants, directly influence parameters of the metabolic syndrome and, in particular, markers of insulin resistance. These findings identify novel genetic determinants of adiponectin levels, which, taken together, influence risk of T2D and markers of insulin resistance.

Materials and Methods

Ethical Consideration

All participants provided informed written consent. The research protocol of all studies were reviewed and approved by institutional ethics review committees at the involved institutions.

Study Design

Our study consisted of three stages. *First*, in the discovery stage we performed a meta-analysis of the GWAS summary statistics of 16 studies involving 29,347 participants of white European origin to detect SNPs that are associated with adiponectin levels. All signals with $p<5\times10^{-6}$ were followed up in seven additional cohorts (n = 6,623) with GWAS data (*in-silico* phase) that later joined the consortium and then a subset of SNPs (n = 10) by *de-novo* genotyping in 3,913 additional participants from three cohorts (n = 39,883 for the combined analysis in Europeans). We also performed a multi-ethnic meta-analysis by combining summary statistics from the 16 studies of individuals of white European discovery cohorts (n = 29,347) with those of five cohort studies that included African Americans subjects (n = 4,232) and one East Asian cohort (n = 1,776) to obtain a total 35,355 individuals for the GWAS meta-analysis involving different ethnicities. After identifying variation near two genes of pharmaceutical importance (*GPR109A* and *GPR109B*), which encode the putative niacin receptors, we typed additional rare coding and tagging variants in a subset of cohorts. *Second*, we examined whether the identified SNPs of the first stage also associate with mRNA levels of nearest gene(s) expressed using adipose tissue of 776 European women. We also tested for association between adiponectin levels and mRNA levels of the genes in our candidate loci in adipose tissue of a subgroup of 436 individuals [25]. *Third*, we calculated a multi-SNP genotypic risk score using genome-wide significant adiponectin-lowering alleles and tested the association of this risk score with T2D and related metabolic traits. Figure 3 shows a flow chart detailing the study design.

Study Populations

In total, 45,891 individuals from 26 European and 7 non-European cohorts participated in the different phases of this meta-analysis. Participating cohorts were either population-based (n = 23), family-based (n = 4), or case-control (n = 4) studies. The age of participants ranged from 10 to 95 years. Adiponectin levels were measured using ELISA or RIA methods. More details on the study cohorts and adiponectin measurement are presented in the Text S1 and Table S1. In addition, genotyping of four coding and tagging SNPs in the candidate genes, *GRP109A* and *GPR109B*, was undertaken in samples from the Lausanne, Lolipop, MRC Ely, and Fenland cohorts.

Genotyping and Imputation

All cohorts were genotyped using commercially available Affymetrix or Illumina genome-wide genotyping arrays. Quality control was performed for each study independently and genotype imputation was carried out using IMPUTE, MACH, BimBam or Beagle with reference to either the Phase II CEU, CEU+YRI, or CHB+JPT+CEU HapMap according to the origin of population. Imputation of East Asian genotypes was undertaken by first masking genotypes of 200 SNPs and then imputing them based on the CEU+CHB+JPT panel from HapMap. This resulted in an allelic concordance rate of ~96.7%. For the African Americans, a combined CEU+YRI reference panel was created. This panel included SNPs segregating in both CEU and YRI, as well as SNPs

segregating in one panel and monomorphic and non-missing in the other (2.74 million SNPs). Due to the overlap of African American individuals on the Affymetrix 6.0 and IBC arrays [51], it was possible to analyze imputation performance at SNPs not genotyped on Affymetrix 6.0. For imputation based on Affymetrix data, the use of the CEU+YRI panel resulted in an allelic concordance rate of ~95.6% (calculated as 1−0.5 * [imputed_dosage– chip_dosage]). This rate is comparable to rates calculated for individuals of African descent imputed with the HapMap 2 YRI individuals. Table S1 summarizes the genotyping methods used for each cohort, genotype-calling algorithms, imputation algorithms and exclusion thresholds. SNP-level quality control metrics were applied prior to meta-analysis for each cohort. These were: call rate ≥95%, minor allele frequency (MAF)≥1%, Hardy-Weinberg equilibrium (HWE) $p>10^{-6}$, and quality measures for imputed SNPs (r^2≥0.3, or proper info ≥0.4, for cohorts imputing their data with MACH and IMPUTE, respectively).

Eleven coding and tagging variants in two candidate genes of pharmaceutical importance (*GPR109A* encoding the niacin receptor and *GPR109B*) were genotyped in a parallel study in Lausanne, Lolipop, MRC Ely, and Fenland white subjects. Genotyping was performed using a KASPar-On-Demand SNP Genotyping Assay (KBioscience Ltd., Hoddesdon, UK). In Lausanne and Lolipop samples the genotyping assay was carried out on 3.75 ng of genomic DNA in 1 µl 1536-well plate reactions, dispensed with a Meridian, microfluidic dispenser (KBioscience Ltd., Hoddesdon, UK), thermocycled using a Hydrocycler (KBioscience Ltd., Hoddesdon, UK). A Pherastar (BMG GmbH, Germany) was used for end-point detection and Kraken-LIMS (KBioscience Ltd., Hoddesdon, UK) was used for automated allele calling. In MRC Ely and Fenland samples, the genotyping assay was carried out on 10 ng of genomic DNA in 5 µl 384-well plate reactions using a G-Storm GS4 Thermal Cycler (GRI, Rayne, UK). The ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Warrington, UK) was used for end-point detection and allele calling.

Statistical Analysis

Genome-wide association studies. All cohorts independently tested for the additive genetic association of common (MAF>1%) genotyped and imputed SNPs with natural log transformed adiponectin levels, while adjusting for age, sex, body mass index (BMI), principal components of population stratification and study site (where appropriate), and for family structure in cohorts with family members [49,50,52]. The analyses were performed for men and women combined, as well as for men and women separately. The Cardiovascular Health Study cohort (CHS) also provided GWA results for high molecular weight (HMW) adiponectin using the same methods as described above.

Meta-analysis of GWAS. The meta-analysis was performed by two analysts independently each using different methods; inverse variance-weighted methods using both fixed and random effect models available through either the METAL (http://www.sph.umich.edu/csg/abecasis/metal/) or GWAMA version 2.0.5 (http://www.well.ox.ac.uk/gwama/) software packages [53]. Summary statistics were crosschecked to ensure consistency of results. Prior to the meta-analysis, study-specific summary statistics were corrected using genomic control (lambda range = 0.99–1.25) and the overall meta-analytic results were additionally corrected for genomic control (lambda = 1.06). To examine whether associations with adiponectin were sex-specific, we performed meta-analyses for men and women separately. A *p*-value threshold of 5×10^{-8} was considered to be genome-wide significant. Ethnicity-specific meta-analyses were performed for white European and non-European populations separately, using the same methods as described above.

Presence of heterogeneity in the meta-analysis was assessed by the I^2 statistic and Q-test [54]. Since cohorts measured adiponectin concentrations using either RIA or ELISA methods, we also performed a GWA meta-analysis stratified by the method of measurement to test whether this contributed to heterogeneity.

Follow-up phase. The follow-up phase comprised two stages; *in-silico follow-up* and *de-novo follow-up*.

—In silico follow-up: 468 SNPs with $p<5\times10^{-6}$ from the discovery phase (which includes both genome-wide significant [n = 196, $p<5\times10^{-8}$] and "suggestive" [n = 272, $5\times10^{-8}<p<5\times10^{-6}$] SNPs Table S3) were tested for their association in 6,623 individuals from seven additional cohorts with GWAS data that joined the consortium after the discovery stage had been finalized.

—De novo follow-up: We next selected the lead SNP arising from selected loci from the joint analysis of the discovery and *in-silico* follow-up phase with p-values greater than 5×10^{-8} but less than 5×10^{-6} and genotyped 10 SNPs in 3,164 samples from the SAPHIR cohort and an additional subgroup of the KORA cohort. Finally, these same SNPs, or their proxy SNPs (n = 2), were tested for association in the THISEAS cohort (n = 738), which had been genotyped using the Metabochip [55]. Study-level summary statistics from the follow-up phases were meta-analyzed with the data from the discovery phase.

Multi-ethnic meta-analysis. In order to perform a meta-analysis of GWAS data from cohorts of different ethnic backgrounds, we utilized the novel MANTRA (Meta-ANalysis of Trans-ethnic Association studies) software [24]. This method combines GWAS from different ethnic groups by taking advantage of the expected similarity in allelic effects between the most closely related populations. Fixed-effects meta-analysis assumes the allelic effect to be the same in all populations, and cannot account for heterogeneity between ethnic groups. Conversely, random effects meta-analysis assumes that each population has a different underlying allelic effect, however, populations from the same ethnic group would be more homogeneous than those that are more distantly related. To address this challenge we accounted for the expected similarity in allelic effects between the most closely related populations by means of a Bayesian partition model. For each variant, allelic effects and corresponding standard errors are estimated within each population under the assumption of an additive model. Populations are then clustered according to their similarity in terms of relatedness as measured by the mean allele frequency difference at 10,000 independent SNPs, and to their allelic effects at the variant. If all populations are assigned to the same cluster, this is equivalent to a fixed allelic effect across all populations (i.e. no trans-ethnic heterogeneity). The posterior distribution of the allelic effect in each population under the Bayesian partition model is approximated by means of a Monte-Carlo Markov chain algorithm. Evidence in favor of association of the trait with the variant was assessed by means of a Bayes' factor (BF). A log10 BF of 6 or higher is considered a relatively conservative threshold for genome-wide significance. We also performed meta-analysis by using both random and fixed effects models including all ethnicities. Those loci that achieved both a BF>6 in MANTRA and a P-value less than 5×10^{-7} in multiethnic analysis are presented in Table 2.

Association of Genome-Wide Significant SNPs with Gene Expression (Stage 2)

In order to identify *cis*-expression quantitative trait loci (*cis*-eQTLs) and test whether mRNA levels of candidate genes arising from our GWAS were associated with adiponectin levels, we used

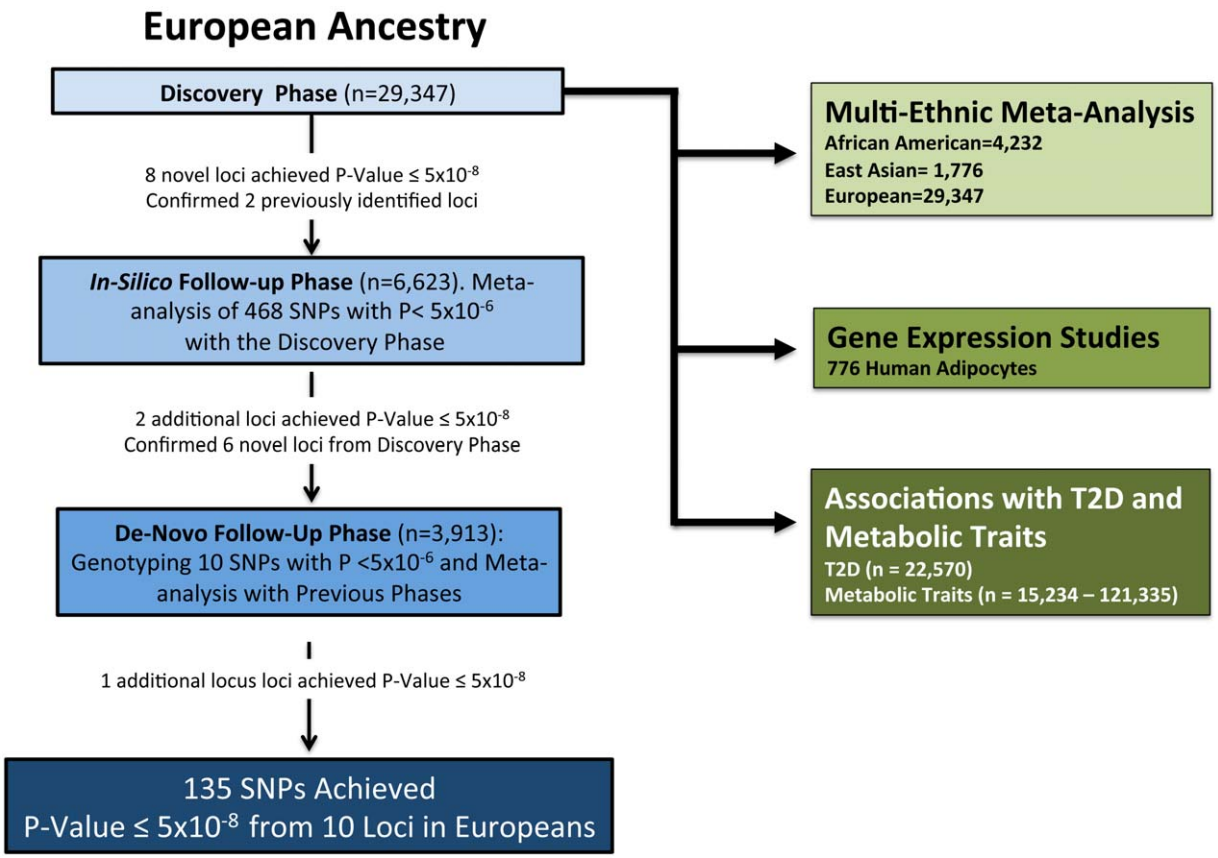

Figure 3. Flow chart of study design.
doi:10.1371/journal.pgen.1002607.g003

expression profiles in human adipocytes from the Multiple Tissue Human Expression Resource (MuTHER) Consortium, (856 female twins from the UK) [25]. mRNA expression profiles from subcutaneous fat and genome-wide genotypes were available for 776 individuals and circulating adiponectin levels for 436 of these women. We note that while adiponectin levels were measured at an earlier time point than the fat biopsies, the BMI at time of adipose expression measurement and time of adiponectin measurement was highly correlated ($r^2 = 0.9$).

cis-eQTLs were defined as associations between SNPs and a transcript within 1 Mb of the identified SNP. To correct for multiple testing, we used QVALUE software [56], and estimated that a genome-wide false discovery rate of 1% corresponds to a *p*-value threshold of 5.06×10^{-5} (this conservative threshold accounts for all multiple arising from the use of the array, rather than multiple testing arising from assessing only transcripts in the genome-wide significant regions). To test whether mRNA levels of candidate genes identified in the GWAS meta-analysis are associated with circulating adiponectin levels, we applied a Bonferoni corrected threshold of $p<3\times10^{-4}$ (where $3\times10^{-4} = 0.05/133$ and 133 was the number of transcripts tested at the candidate loci).

Association of Genome-Wide Significant SNPs with T2D and Metabolic Traits (Stage 3)

The DIAGRAM+ (effective n = 22,044) [19], MAGIC (n = up to 46,186) [20], GLGC (n = up to 97,021) [22], GIANT (n = up to 121,335) [21], and Body Fat GWAS (n = up to 36,625) consortia provided summary statistics for the association of each SNP that was genome-wide significant in the discovery phase. Since 196 SNPs (which were estimated to be equivalent to 96 independent statistical tests due to linkage disequilibrium [LD]) [26] were tested for their association, we employed a Bonferroni-corrected threshold of $\alpha = 0.0005$ (where $0.0005 = 0.05/96$) to define the threshold of association for any individual SNP association with T2D and related traits.

While any individual SNP may demonstrate a relationship with T2D or related traits, it can be more informative to test whether a multi-SNP genotypic risk score is associated with the outcome of interest. In the absence of pleiotropic effects arising from loci other than *ADIPOQ*, such a multi-SNP genotypic risk score would enable testing of whether adiponectin levels are causally related to risk of T2D or metabolic traits through a Mendelian randomization framework. Since most of the SNPs that we identified to be genome-wide significant for adiponectin levels were not in the *ADIPOQ* locus, the presence of such pleiotropy precluded a formal Mendelian randomization study. To create a multi-SNP genotypic risk score we implemented a novel method that approximates the average effect of adiponectin decreasing alleles on T2D or related traits. Further, this method allows the use of consortium-level meta-analytic results for a set of SNPs, rather than requiring the re-analysis of individual-level data in each cohort, thereby providing more accurate effects of each allele (due to the larger sample size in the consortium-level meta-analysis). The weighted sum of the individual SNP coefficients leads not only to an estimate of the average combined allelic effect, but also to an approximate estimate of the explained variance (when scaled by the inverse of the total meta-analysis sample size) from a multivariate regression model containing these SNPs.

Specifically, suppose m SNPs have shown association in the discovery phase, and effects are denoted w_i. However, suppose that the goal of interest is to estimate the joint effect of these SNPs on an outcome of interest, y. Let j index the individuals in the outcome of interest dataset and let

$$s_j = \sum_{i=1}^{m} w_i x_{ij}$$

be a risk score based on the discovery data SNPs, and their associated parameter estimates w_i. Therefore, the desired goal is to estimate the parameter in the following equation: $y_j = y_0 + as_j + e_j$ in the outcome of interest dataset. The proportion of variance in y explained by the previous equation, (i.e. the R^2) attributable to the risk score can be estimated. Standard linear model theory shows that the change in log likelihood is proportional to the R^2,

$$2[\ln L(M_1) - \ln L(M_0)] \cong nR^2$$

If the SNPs are uncorrelated, and if the total percentage of variance explained is small, then the change in log likelihood can be approximated by

$$C - \sum_{i=1}^{m} \frac{\left(\beta_i - \hat{\beta}_i\right)^2}{2s_i^2}$$

where β_i now refers to the effect of SNP i in the outcome data, $\hat{\beta}_i$ is the outcome data estimate, and s_i is the associated standard error estimate. Assuming that this log likelihood difference approximation is maximized with an appropriate value of C, then it can be shown that a can be estimated by:

$$\hat{a} \cong \frac{\sum_{i=1}^{m} w_i \hat{\beta}_i s_i^{-2}}{\sum_{i=1}^{m} w_i^2 s_i^{-2}}$$

with a standard error estimate of

$$se(\hat{a}) \cong \sqrt{\frac{1}{\sum_{i=1}^{m} w_i^2 s_i^{-2}}}$$

Therefore, under the assumption of uncorrelated SNPs, their joint effect can be estimated in external data by a weighted mean of the individual SNP effects, weighted by the estimates from the discovery data. All these quantities can be obtained from meta-analysis or summary data, so that individual-level data are not required to obtain these results.

To implement this method, we first selected LD-independent adiponectin associated alleles by LD pruning the set of genome-wide significant adiponectin SNPs from the discovery phase with an LD threshold of $r^2 \leq 0.05$ in the HapMap CEU population, yielding 20 independent LD blocks from the 196 SNPs in Table S2. (We also applied the method using an LD threshold of $r^2 \leq 0.01$ and found no relevant change in results). Since many SNPs from the same independent blocks were associated with adiponectin, we selected the SNP from the LD block that explained the most variance in adiponectin levels. Next, we approximated the effect of the multi-SNP genetic risk score using β and its standard error as derived from the consortium-level meta-analysis in DIAGRAM+, MAGIC, GLGC, GIANT and Body Fat GWAS consortium.

Supporting Information

Figure S1 The comparison between two independent meta-analyses performed in different centers for quality control purposes. The $-\log 10$ p-value of all SNPS with MAF$\geq$0.01 in the first analysis are plotted against the $-\log 10$ p-value from the second analysis.
(TIF)

Figure S2 The Manhattan plots of sex-stratified meta-analyses in the discovery phase in the European population. The meta-analysis shown in panel a) is stratified for women and that in panel b) is stratified for men. Manhattan plots demonstrate $-\text{Log}_{10}(p\text{-value})$ measures for association between single nucleotide polymorphisms (SNPs) and chromosomal position. The SNPs that achieved genome-wide significance are highlighted in green in the plots. The red ovals identify loci found only in women.
(TIF)

Figure S3 Association Results Near Peaks for Sex-specific Analysis of Adiponectin. SNPs in regions near peak associations are shown for a) chromosome 8 female, b) chromosome 8 males, c) chromosome 12 females and d) chromosome 12 males. Purple diamonds indicate the top SNPs, which have the strongest evidence of association in women. Each circle shows a SNP with a color scale proportional to the r^2 value for that SNP and the top SNP from HapMap CEU. Blue lines show the estimated recombination rates from HapMap. The bottom panels illustrate the relative position of each gene in the locus.
(TIF)

Table S1 Cohort characteristics.
(XLSX)

Table S2 Comparing the Genome-Wide Significant SNPS from fixed effect model with random effect model. *SNP with I^2 less than 0.5 are listed in bold, EA: Effect Allele, NEA: Non-Effect Allele.
(PDF)

Table S3 Association Results of SNPs achieving $p \leq 5\times10^{-6}$ in the Discovery phase in European Populations (Sex-Combined Analysis). *Denotes SNPs typed in the *de-novo* follow-up phase.
(PDF)

Table S4 Genome-Wide Significant SNPs ($p<5\times10^{-8}$) Associated with Adiponectin Levels in Non-Europeans Populations. EA: Effect Allele, NEA: Non-Effect Allele, EA-Freq: Frequency of Effect Allele.
(PDF)

Table S5 SNPs associated with adiponectin at genome-wide significant levels ($p<5\times10^{-8}$) using the fixed-effect model in women only in European populations (including Discovery and Follow-Up phases).
(PDF)

Table S6 SNPs associated with adiponectin at genome-wide significant levels ($p<5\times10^{-8}$) using fixed-effect models in men only in Euopean populations.
(PDF)

Table S7 Association results of nominally significant SNPs with Type 2 Diabetes in the DIAGRAM+ Consortium. EA: Effect Allele, NEA: Non-Effect Allele. B) Association results of nominally significant SNPs with diabetes-related traits in the MAGIC Consortium. Fasting glucose and 2 h glucose in mmol/L; Insulin in pmol/L, EA: Effect Allele, NEA: Non-Effect Allele. C) Association results of nominally significant SNPs with diabetes-

related traits in the GIANT and Body fat GWAS consortia. The beta expressed in inverse normally transformed BMI units (i.e. interpretable as SD or Z-score), shows the change in BMI per additional effect allele.,*Results that are statistically significant, accounting for the number of independent SNPs, are highlighted in bold., EA: Effect Allele, NEA: Non-Effect Allele, EA-Freq: Frequency of Effect Allele. D) Association results of nominally significant SNPs with lipid traits in the GLGC Consortium. For these traits the effect size is in SD units, based on standard error-weighted meta-analysis. *Results that are statistically significant, accounting for the number of independent SNPs are highlighted in bold., EA: Effect Allele, NEA: Non-Effect Allele, EA-Freq: Frequency of Effect Allele.
(PDF)

Text S1 Supplemental data include description of study cohorts and funding.
(DOCX)

Acknowledgments

We thank all study participants, volunteers, and study personnel that made this consortium possible. We would also like to thank Ms. Renee Atallah for her efforts with the writing and correction of the manuscript.

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